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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/524,147

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EXAMINER

COVINGTON, RAYMOND K

ART UNIT

PAPER NUMBER

1625

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DELIVERY MODE

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/524,147	<b>Applicant(s)</b> MATUSZCZAK ET AL.	
	<b>Examiner</b> Raymond Covington	<b>Art Unit</b> 1625	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 11 February 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-20 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/11/05</u> .   | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-20 provides for the use of a chemical compound, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 17-20 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear whether the terms, Het, Het radical and Het- substituted, are drawn to hetero atoms, such as O, S or N, or to heterocyclic groups such as furan or pyridine.

Claims 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrases, bioprecursor-carrier and function that is characteristic of the bioprecursor, are confusing, indefinite as to what they mean.

Claims 11 and 15-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase, physiologically harmless, is confusing, indefinite as to what they mean.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase variable pharmaceutical active, indefinite as it reads on essentially no activity, e.g. 0.00000000000001% activity.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for indole and chroman substituted tocopherol compounds, does not reasonably provide enablement for the broader scope encompassed by Het, heterocyclic heteroaryl and claims dependent thereon. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Specification provides no guidance as to what other rings might be suitable and there is no basis in the prior art directed to similar compounds having the same activity as herein.

Scope of 5- to 10-membered heteromonocyclic heteropolycyclic having 1 to 4 heteroatoms is not adequately enabled. A review of the specification shows only 2 rings for heteroaromatics described that are representative of actual working examples.

The limited data provides no clear evaluation of how the remaining scope with up to 4 hetero atoms in any array and degree of unsaturation might affect potency to a large or small degree.

Applicants have failed to establish that the compounds tested are structurally and functionally similar to those tested herein or to known compounds having the same activities.

There is thus no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent . Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure- sensitive arts such as the pharmaceutical art. Also note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a), August 2000 edition. Thus given the breadth of the claims, the level of unpredictability in the art and the lack of direction (i.e. working examples) provided as to what other ring systems might work this rejection is applied.

Though clearly one of ordinary skill in the art could identify much of what is within the scope of the  $R^1$ ,  $R^3$ ,  $R^4$ ,  $R^6$ ,  $R^7$  etc. the delineation between what is and what is not claimed has not been circumscribed. That is, all of what is claimed is

not identifiable. The specification does not limit "heterocyclic" to any particular definition. See, for example page 11 of the specification. Again, where the delineation between claimed subject matter and unclaimed subject matter lies is unclear from a reading of the claims in light of the specification. More than one definition of the general term "heterocyclic" or "heterocycle" is accepted by those of ordinary skill in the art of organic chemistry. Some consider cyclic organic compounds wherein at least one carbon atom is replaced by sulfur, oxygen or nitrogen to be heterocyclic compounds, while others of ordinary skill include selenium, tellurium, boron or tin containing rings to be within the scope of the term "heterocyclic" as it is commonly used, and some definitions of "heterocyclic" do not require carbon to be present at all.

The examiner directs applicants' attention to the following three references:

On page 282 of the McGraw--Hill Dictionary of Chemical Terms (1990), the definition of "heterocyclic compound" is a compound in which the ring structure is a combination of more than one kind of atom. On page 490 of the Concise Encyclopedia Chemistry (1993), the definition of "heterocycles" is cyclic hydrocarbon compounds in which the ring consists of carbon and at least one other element, usually, N, O or S. The definition goes on to explain that the possibilities for synthesis are nearly unlimited, and that compounds wherein the heteroatoms

are of elements like phosphorous, arsenic, selenium, and tellurium are being incorporated with increasing frequency. On page 594 of Hawley's Condensed Chemical Dictionary (1993), "heterocyclic" is defined as a closed-ring structure, usually, either 5 or 6 members, in which one or more of the atoms in the ring is an element other than carbon, e.g, sulfur, nitrogen, etc. These three definitions should make it abundantly clear that there is no one specific and exact definition of the word "heterocyclic," thus when this term is present as a claim limitation, the metes and bounds of protection are not pointed out and distinctly claimed. Though the three above-cited definitions of the term have some shared aspects, chemists of ordinary skill would not necessarily agree on the full scope and meaning of the term "heterocyclic."

Claims 11- 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for salts of the claimed compounds, does not reasonably provide enablement for prodrugs or solvates of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples,



d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation. Determining if any particular substrate would form a solvate would require synthesis of the substrate and subjecting it to recrystallization with a variety of solvents, temperatures, pressures, and humidity. The experimentation is potentially open-ended.

b) The direction concerning the prodrugs and solvates is found in pages 23, 25 and 33. c) The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 “The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist.” The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

d) The nature of the invention regarding prodrugs is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. The nature of the invention regarding solvates is chemical synthesis, which involves chemical reactions. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second

paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. In the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry

of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stable region of the solvate. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. The artisan using Applicants invention to prepare the claimed compounds would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State

Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stable region of the solvate.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I as well as the presently unknown list of potential prodrug derivatives and/or solvates embraced by claims 11-20.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the

time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular compound is, in fact, a prodrug or solvate.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-12 and 15-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamamoto et al US 4914197, Ogata US 4742163 or Weischer et al DE 4333794.

Yamamoto et al, Ogata or Weischer et al all teach tocopherol compounds corresponding to applicants’ formula I. See respectively, column 1 lines 42-60, column 2 lines 10+ formula I and page 10 lines 5-15.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al US 4914197, Ogata US 4742163 or Weischer et al DE 4333794.

Yamamoto et al, Ogata or Weischer et al all teach tocopherol compounds corresponding to applicants' formula I. See respectively, column 1 lines 42-60, column 2 lines 10+ formula I and page 10 lines 5-15.

As to claim 13 formation of a salt would be an obvious derivation well within the ordinary skill of one in this art.

As to claim 14, characteristic being open language, the claim reads on known prior art of record.

As to claim 15, isolated forms would have been an obvious expedient to one of ordinary skill in the art.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond Covington whose telephone number is (571) 272-0681. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres at telephone number (571) 272-0867.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/R. C./  
Examiner, Art Unit 1625  
RKC

/Janet L. Andres/  
Supervisory Patent Examiner,  
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